Amendments to the Specification:

Please replace paragraph [0004] on pages 2-3 with the following amended paragraph:

[0004] Trastuzumab (~~Herceptin™~~ HERCEPTIN™) is a humanized monoclonal antibody specifically binding to HER2/c-erbB-2 protein. Trastuzumab (~~Herceptin™~~ HERCEPTIN™) targets HER2/c-erbB-2 protein-overexpressing tumor cells to specifically bind. The binding inhibits the receptor function of HER2 / c-erbB-2 protein, thereby to inhibit signal transmission, effecting in the inhibition of tumor cell proliferation. Therefore, the identification of patients to be treated with trastuzumab (~~Herceptin™~~ HERCEPTIN™) requires the examination of overexpression of HER2/c-erbB-2 protein or situation of c-erbB-2 gene amplification in cancer tissues (non-patent document No.4).

Please replace paragraph [0008] on page 4 with the following amended paragraph:

[0008] In evaluation of expression of HER2/c-erbB-2 according to the standard described above, treatment with trastuzumab (~~Herceptin™~~ HERCEPTIN™) is evaluated in case of 3+ to be effective, but in cases of 2+ to be ambiguous. In summary, treatment with trastuzumab (~~Herceptin™~~ HERCEPTIN™) is certainly confirmed to be effective in case of 3+, but is not always effective in case of 2+. On the other hand, positive staining given according to FISH method shows that treatment with trastuzumab (~~Herceptin™~~ HERCEPTIN™) is ensured to be effective at a certain rate.

Please replace paragraph [0011] on pages 5 with the following amended paragraph:

[0011] Immunohistochemical analysis and FISH method were compared on effectiveness of examination for HER2 / c-erbB-2 expression. As a result, a conclusion was obtained that FISH method is better than immunohistochemical analysis in reproducibility and allows more accurate evaluation of expression state of HER2/c-erbB-2. Further, it is known that the rate of cases effectively treated with trastuzumab (~~Herceptin™~~ HERCEPTIN™) in the positive cases is higher by the FISH method than by the immunohistochemical analysis. However, as the FISH method is laborious and costly, therefore a conclusion was obtained that the FISH method should be performed to determine effectiveness of treatment with trastuzumab (~~Herceptin™~~

HERCEPTIN™) only for the cases of 2+ shown by the immunohistochemical analysis (non-patent document No.5).

Please replace paragraph [0014] on page 6 with the following amended paragraph:

[0014] To solve the problems described above, the present inventor studied to find an examination method for accurately evaluating the effectiveness of trastuzumab (~~Herceptin™~~ HERCEPTIN™) which is an anticancer drug targeting HER2/c-erbB-2 of tumor-associated factor receptor.

Please replace paragraphs [0015] and [0016] on page 7 with the following amended paragraph:

[0015] Currently, the effectiveness of trastuzumab (~~Herceptin™~~ HERCEPTIN™) is evaluated by examining overexpression of HER2 / c-erbB-2, for example, through the immunohistochemical analysis and the FISH method. In the above examination methods, proteins are determined to be positive only if stained in a cell membrane, but negative if stained only within the cytoplasm. Here, treatment with trastuzumab (~~Herceptin™~~ HERCEPTIN™) to work effective needs that overexpressed HER2/c-erbB-2 is present functionally as a receptor on the cell membrane. Therefore, the inventor thought that, even if the examination methods as described above show the overexpression of c-erbB-2 gene and a large production of HER2/c-erbB-2, no HER2/c-erbB-2 anchored successfully on the cell membrane would suggest no expected effectiveness of treatment with trastuzumab (~~Herceptin™~~ HERCEPTIN™).

[0016] Further, a fairly diverse of cancers are recognized to overexpress HER2/c-erbB-2 at a high frequency. Currently, treatment with trastuzumab (~~Herceptin™~~ HERCEPTIN™) has been put into practical use in breast cancer, but has given a too low proportion of effective cases for cancers in the other organs to be put into practical use. As the cause, the inventor estimated that overexpressed HER2/c-erbB-2 was unlikely to function on the cell membrane. Thus, the inventor has thought it to be quite useful for estimating therapeutic effects with trastuzumab (~~Herceptin™~~ HERCEPTIN™) on an individual cancer that a substance, which is important for HER2/c-erbB-2 to function well on the cell membrane and interacts with the HER2/c-erbB-2 on the surface of and/or within the cell membrane, is examined beforehand to determine whether the substance is present or not in the cancer.

Please replace paragraph [0017] on page 8 with the following amended paragraph:

[0017] Thus, on cancer cases with overexpressed HER2/c-erbB-2 and treated with trastuzumab (~~Herceptin™~~ HERCEPTIN™), MUC4, that is, a substance which interacts with HER2/c-erbB-2 on the surface of and/or within cell membrane and makes the HER2/c-erbB-2 function effectively as a receptor on the cell membrane, was examined to clarify the relation between the expression state of the substance and the effectiveness of treatment with trastuzumab (~~Herceptin™~~ HERCEPTIN™).

Please replace paragraph [0019] on page 10 with the following amended paragraph:

[0019] In summary, the present invention is composed of the followings:

1. An examination method conducted for the administration of an anticancer drug targeting a tumor-associated factor receptor, in order to evaluate usefulness of treatment with the anticancer drug, comprising, in addition to the examination of the gene and/or the expressed product thereof of the receptor, the examination of the gene and/or the expressed product thereof of a substance interacting with the receptor on the surface of and/or within the cell membrane.
2. The examination method according to the preceding clause 1, wherein the tumor-associated factor receptor is a cell growth factor receptor.
3. The examination method according to the preceding clause 2, wherein the cell growth factor receptor is an epidermal growth factor receptor or a receptor belonging to an epidermal growth factor receptor family.
4. The examination method according to the preceding clause 3, wherein the receptor belonging to the epidermal growth factor receptor family is HER2/c-erbB-2.
5. The examination method according to anyone of the preceding clauses 1 to 4, wherein the substance interacting with the receptor on the surface of and/or within cell membrane is a glycoprotein.
6. The examination method according to the preceding clause 5, wherein the glycoprotein is a mucin.
7. The examination method according to the preceding clause 6, wherein the mucin is mucin 4 (MUC4).

8. The examination method according to anyone of the preceding clauses 1 to 7, wherein the anticancer drug is an antibody to the receptor.

9. The examination method according to the preceding clause 8, wherein the antibody is a humanized monoclonal antibody.

10. The examination method according to the preceding clause 9, wherein the humanized monoclonal antibody is trastuzumab (~~Herceptin™~~ HERCEPTIN™).

11. A reagent for use in the examination method according to anyone of the preceding clauses 1 to 10.

12. A reagent kit for use in the examination method according to anyone of the preceding clauses 1 to 10.

Please replace paragraph [0027] on page 14 with the following amended paragraph:

[0027] The anticancer drug is preferably an antibody to a product involved in a signal transmission system, and more preferably a humanized monoclonal antibody. The product involved in a signal transmission system includes a receptor, thus an antibody to the receptor may be mentioned as an example. As the typical receptor, HER2/ c-erbB-2 may be mentioned. Further, trastuzumab (~~Herceptin™~~ HERCEPTIN™) which is a humanized monoclonal antibody to HER2/c-erbB-2 may preferably be mentioned. Besides them, as the agent for molecular targeting therapy, which is an anticancer drug of the present invention, ZD1839 (~~Iressa™~~ IRESSA™), STI-571 and the like may be mentioned. ZD1839 (~~Iressa™~~ IRESSA™) is an inhibitor against the tyrosine kinase activity of EGFR, and STI-571 is an inhibitor against the tyrosine kinase activity of BCR-Abl and c-kit.

Please replace paragraph [0029] on page 16 with the following amended paragraph:

[0029] As the gene encoding a product involved in signal transmission system, a gene directing a cell to get cancerous may be mentioned. Such gene includes, but not limited to, a gene having a growth factor function such as sis, int-2 and hst; a gene having a receptor-typed tyrosine kinase function such as erbB, erbB-2/neu, ros, fms, kit and ret; a gene having a nonreceptor-typed tyrosine kinase function such as src, yes, fgr, lck, fps/fes and abl; a gene having a serine/threonine kinase function such as c-raf; the other gene like ras, bcl, int-1 and

crk; and an intranuclear protein such as myc, fos, j un and erbA. Substances inhibiting the functions of some of these genes or functions of the expressed products thereof have been developed and used for pharmaceutical purposes. As the typical and preferred example, trastuzumab (~~Herceptin™~~ HERCEPTIN™) used as an antibody agent against HER2/c-erbB-2 which is the gene product of erbB-2/neu may be mentioned.

Please replace paragraph [0038] on page 20 with the following amended paragraph:

[0038] As one example, HER2/c-erbB-2 is overexpressed not only in breast cancer but also in many cancers, but it is examined to make a practice of the treatment only for breast cancer. This is because the treatment has shown low effectiveness in high HER2/c-erbB-2 expressing cancers except breast cancer. For example, in colon cancer, HER2/c-erbB-2 is overexpressed at a high frequency, but MUC4 is found to be basically negative in colon epithelium including the tumor's, causing the treatment hardly to exhibit effectiveness. However, some cancers of MUC4 positive organs express HER2/c-erbB-2 at a high level. From cases of those cancers, a case which expresses both MUC 4 and HER2/c-erbB-2 is selected to treat with trastuzumab (~~Herceptin™~~ HERCEPTIN™). The case can be evaluated to be likely treated by high effectiveness. Therefore, the combination of the examinations for MUC4 and HER2/c-erbB-2 can broaden an applicable range for treatment with trastuzumab (~~Herceptin™~~ HERCEPTIN™).

Please replace paragraph [0041] on pages 21-22 with the following amended paragraph:

[0041] EXAMPLE 1

With cases where HER2/ c-erbB-2 were detected in tissues of breast cancer patients by immunohistochemical staining described above, the relation between therapeutic effects with trastuzumab (~~Herceptin™~~ HERCEPTIN™) and stainability of MUC4 shown by immunohistochemical analysis was studied.

As a result, such results as shown in Table 1 were obtained. Among six cases which had an HER2/ c-erbB-2 score of (++) or more, MUC4 positive were three wherein one was (+++) and two were (++). From these results, it was revealed that there were no mutual relations between HER2/c-erbB-2 and MUC4 expressions. Therefore, it was suggested to be meaningful to examine HER2/c-erbB-2 and MUC4 respectively.

Among three HER2/c-erbB-2 positive (+++) cases, one completely remitted case was MUC4 posi tive, one case showing no or poor effect was MUC4 negative, and one case rejected treatment with trastuzumab (~~Herceptin™~~ HERCEPTIN™). Both two HER2/c-erbB-2 positive (++) cases were MUC4 positive, one example of which was treated with trastuzumab (~~Herceptin™~~ HERCEPTIN™) to show complete remission, although another was not treated with trastuzumab (~~Herceptin™~~ HERCEPTIN™) because it was on an early stage.
From the facts above, it was revealed that a parallel relation did not always exist between MUC4 and HER2/c-erbB-2 expressions, and cases of MUC4 positive and HER2/c-erbB-2 positive (++) or more showed good responses to trastuzumab (~~Herceptin™~~ HERCEPTIN™), while cases of MUC4 negative showed poor effects of treatment with trastuzumab (~~Herceptin™~~ HERCEPTIN™) though they were HER2/ c-erbB-2 posi tive. Therefore, it was found that therapeutic effects with trastuzumab (~~Herceptin™~~ HERCEPTIN™) can be predicted by the combination of the examinations for HER2/ c-erbB-2 and MUC4.

Please replace paragraph [0042] on page 23 with the following amended paragraph:

[0042] [Table 1]

Type of Breast Cancer	HER2/c-erB-2	MUC-4	Therapeutic Effects with Trastuzumab (~~Herceptin™~~ HERCEPTIN™)
Papillotubular Carcinoma	(-)	(-)	Not Adapted
Papillotubular Carcinoma	(-)	(+)	Not Adapted
Papillotubular Carcinoma	(-)	(-)	Not Adapted
Scirrhous Carcinoma	(-)	(-)	Not Adapted
Scirrhous Carcinoma	(+++)	(-)	Poorly effective, thus the patient rejected the continuation of therapy and died.
Papillotubular Carcinoma	(+++)	(-)	Not effective. Note: after effects were shown by tamoxifen and ~~Herceptin™~~ trastuzumab (HERCEPTIN™), tamoxifen was eliminated, causing the disappearance of effects.
Papillotubular Carcinoma	(+++)	(+)	Completely Remitted
Papillotubular Carcinoma	(+++)	(-)	Not Effective
Papillotubular Carcinoma	(++)	(+)	Completely Remitted
Papillotubular Carcinoma	(++)	(+)	Not Treated
Scirrhous Carcinoma	(+)	(-)	Not Treated

Papillotubular Carcinoma	(+)	(-)	Not Treated
Papillotubular Carcinoma	(+)	(+)	Not Treated